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(54) Title: ANTITUMOR COMPOSITION CONTAINING A SYNERGISTIC COMBINATION OF AN ANTHRACYCLINE DERIVATIVE WITH A CAMPTOTHECIN DERIVATE

(57) Abstract

There are provided the combined use of 4–demethoxy–3'–deamino–3'–aziridinyl–4'–methansulfonyl daunorubicin or 4–demethoxy–N,N–bis(2–chloroethyl)–4'–methansulfonyl daunorubicin and an antineoplastic topoisomerase I inhibitor in the treatment of tumors and the use of 4–demethoxy–3'–deamino–3'–aziridinyl–4'–methansulfonyl daunorubicin in the treatment of brain tumors.

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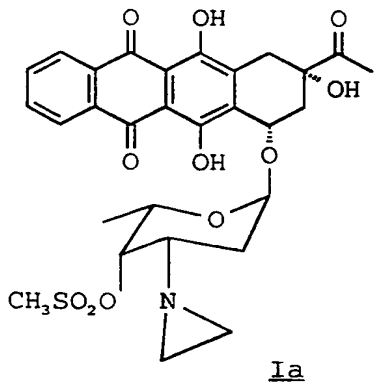
ANTITUMOR COMPOSITION CONTAINING A SYNERGISTIC COMBINATION OF AN ANTHRACYCLINE DERIVATIVE WITH A CAMPTOTHECIN DERIVATE

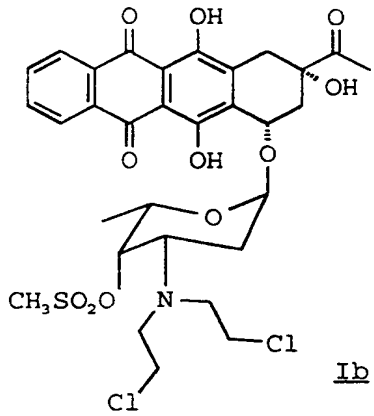
The present invention relates in general to the field of cancer treatment and, more particularly, provides an antitumor composition comprising an alkylating anthracycline and a topoisomerase I inhibitor, having a synergetic antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising

- an anthracycline of formula Ia or Ib :



Ia



Ib

- an antineoplastic topoisomerase I inhibitor, and a pharmaceutically acceptable carrier or excipient.

The chemical names of the anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These anthracyclines were described in Anticancer Drug Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,218 and US-A-5,496,800. Both compounds intercalate into DNA via the chromophore and alkylate guanine at N^7 position in DNA minor groove via their reactive moiety on position 3' of the amino sugar. Compounds

Ia and Ib are able to circumvent the resistance to all major classes of cytotoxics, indicating that the compounds represent a new class of alkylating drugs.

Topoisomerase I inhibitor are described in various scientific publications, see for example the review of M.L. Rothenberg, "Topoisomerase I inhibitors: Review and update", Annals of Oncology, **8**: 837-855, 1997.

Typically, a topoisomerase I inhibitor is camptothecin or its derivative substituted on the quinoline ring or at position 20-OH. Examples of specific topoisomerase I inhibitor to be used in the present invention are: camptothecin, 9-aminocamptothecin, irinotecan (CPT-11), topotecan, 7-ethyl-10-hydroxy-camptothecin, GI 147211 and 9-nitrocamptothecin. All these camptothecin derivatives are known, see for example Medicinal Research Reviws, Vol 17, n° 4, 367-425, 1997. Irinotecan (CPT-11) is the preferred topoisomerase I inhibitor to be used in the present invention. The present invention also provides a product comprising an anthracycline of formula Ia or Ib as defined above and an antineoplastic topoisomerase I inhibitor, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal an anthracycline of formula Ia or Ib as defined above and an antineoplastic topoisomerase I inhibitor, in amounts effective to produce a synergetic antineoplastic effect.

The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a

combination preparation comprising an antineoplastic topoisomerase I inhibitor as defined above and an anthracycline of formula Ia or Ib, as defined above, in amounts effective to produce a synergetic antineoplastic effect.

By the term "a synergetic antineoplastic effect" as used hererin is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, administering an effective amount of the combination of an anthracycline of formula Ia or Ib as defined above and a topoisomerase I inhibitor to mammals, including human.

By the term "administered " or "administering" as used herein is meant parenteral and /or oral administration. By "parenteral" is meant intravenous, subcutaneus and intramuscolar administration. In the method of the subject invention, the anthracycline may be administered simultaneously with the compound with the topoisomerase I inhibitor activity, for example of the camptothecin analog class, or the compounds may be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according to, inter alia, the particular formulation of the anthracycline of formula Ia or Ib being utilized, the particular formulation of the topoisomerase I inhibitor, such as one of the camptothecin analog class, being utilized, the particular tumor model being treated, and the particular host being treated .

In the method of the subject invention, for the administration of the anthracycline of formula Ia or Ib, the course of therapy generally employed is from about 0.1 to about 200 mg/m^2 of body surface area. More preferably, the course

therapy employed is from about 1 to about 50 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the topoisomerase I inhibitor the course of therapy generally employed is from about 1 to about 1000 mg/m^2 of body surface area for about one to about five consecutive days. More preferably, the course therapy employed is from about 100 to about 500 mg/m^2 of body surface area per day for about five consecutive days.

The antineoplastic therapy of the present invention is in particular suitable for treating breast, ovary lung, colon, kidney and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to the preparation of a pharmaceutical composition contaning an effective amount of an anthracycline of formula Ia for the treatment of brain tumors, as well as to the use of an anthracycline of formula Ia for the treatment of brain tumors. As a matter of fact, the anthracycline of formula Ia crosses the blood brain barrier and showed activity against intracranially implanted tumors.

As stated above, the effect of an anthracycline of formula Ia or Ib and a topoisomerase I inhibitor, such as camptothecin derivative, is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline and of the topoisomerase I inhibitor and thus yields the most effective and least toxic treatment for tumors. The superadditive actions of the combination preparation of the present invention are shown for instance by the following *in vivo* tests, which are intended to illustrate but not to limit the present invention.

Table 1 shows the antileukemic activity on disseminated L1210 murine leukemia obtained combining Ia with CPT-11. At the dose of 20 mg/kg of CPT-11 alone (days +1,2) and at the doses of 2.9 and 3.8 mg/kg of Ia alone (day +3) were associated, without toxicity, with ILS% values of 100, 92 and 108, respectively; combining CPT-11 and Ia at the same doses of 2.9 with the same schedule an increase of activity with ILS% values of 375 (with 3/10 cured mice) and >950 (with 8/10 cured mice) was observed, indicating a synergistic effect.

For these experiments Ia was solubilized in [Cremophor® /EtOH= 6.5:3.5]/[normal saline]=20/80 v/v, while CPT-11 was solubilized in water.

Activity against brain implanted tumor model

Brain tumors/metastases are generally unresponsive largely because cytotoxic drugs fail to cross the blood brain barrier. Since data showed that the anthracycline of formula Ia crosses the blood brain barrier, the antitumor efficacy of the anthracycline of formula Ia was tested against intracranially implanted P388 tumor cells in mice. The compound was administered i.v. on days 1,5,9. Results reported in Tab. 2 show that the anthracycline of formula Ia presented good antitumor activity as expressed by ILS% value of 46 at the optimal cumulative dose of 8.1 mg/kg.

Table 1: Antileukemic activity against disseminated L1210[1] of Ia in combination with CPT-11

Compound	Treatment schedule	Dose[2] (mg/kg/day)	ILS%[3]	Tox[4]	LTS[5]
CPT-11	iv+1,2	20	100	0/10	1/10
Ia	iv+3	2.9 3.8	92 108	0/10 0/10	0/10 0/10
CPT-11 + Ia	iv+1,2 iv+3	20 2.9	375	0/10	3/10
CPT-11 + Ia	iv+1,2 iv+3	20 3.8	>950	0/10	8/10

1) L1210 leukemia cells (10^5/mouse) are injected iv on day 0.

2) Treatment is given iv starting on day 1 after tumor transplantation (day 0).

3) Increase in life span : [(median survival time of treated mice/median survival time of controls) x 100] -100.

4) Number of toxic deaths/number of mice.

5) Long Term Survivors (>60 days) at the end of the experiments.

Table 2 Activity against intracranially transplanted P388 murine leukemia[1]

Compound	Dose[2] (mg/kg/day)	ILS% [3]	Tox[4]
Ia	2.1	44	0/20
	2.7	46	1/20

1) P388 leukemia cells (10^4/mouse) injected intracranially on day 0.

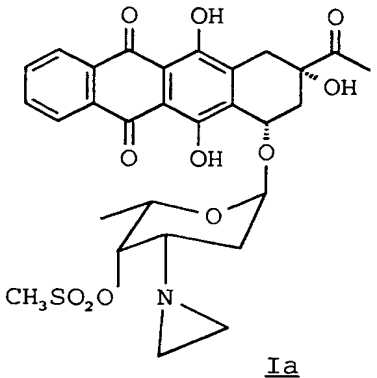
2) Treatment is given i.v. on day 1,5,9 after tumor transplantation (day 0).Ia solubilized in Tween 80 at 10%

3) Increase in life span :[(median survival time of treated mice/median survival time of controls) x 100] -100.

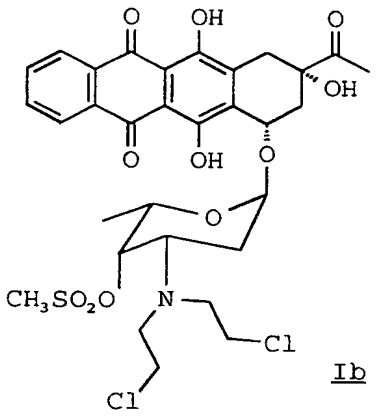
4) Number of toxic deaths/number of mice.

Claims

1. Products containing an anthracycline of formula Ia or Ib:



Ia



Ib

and an antineoplastic topoisomerase I inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. Products according to claim 1 wherein the topoisomerase I inhibitor is camptothecin, 9-aminocamptothecin, irinotecan (CPT-11), topotecan, 7-ethyl-10-hydroxy-camptothecin, GI 147211 or 9-nitrocamptothecin

3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an anthracycline of formula Ia or Ib as defined in claim 1 and an antineoplastic topoisomerase I inhibitor.

4. A composition according to claim 3 wherein the topoisomerase I inhibitor is camptothecin, 9-aminocamptothecin, irinotecan (CPT-11), topotecan, 7-ethyl-10-hydroxy-camptothecin, GI 147211 or 9-nitrocamptothecin

5. Use of an anthracycline of formula Ia or Ib as defined in claim 1 and an antineoplastic topoisomerase I inhibitor in the preparation of a medicament for use in the treatment of tumors.

6. Use according to claim 5 wherein the the topoisomerase I inhibitor is camptothecin, 9-aminocamptothecin, irinotecan (CPT-11), topotecan, 7-ethyl-10-hydroxy-camptothecin, GI 147211 or 9-nitrocamptothecin

7. Use of an anthracycline of formula Ia as defined in claim 1 in the preparation of a medicament for use in the treatment of brain tumors.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01897

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/70 //(A61K31/70,31:47)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZHANG, S. D. ET AL: "Inhibitory effects of homoharringtonine and hydroxycamptothecin in combination with other agents on cancer cell growth" ASIA PAC. J. PHARMACOL., 1992, 191-5, XP002112006 abstract page 195, line 3 - line 7 ---	1-6
Y	EDER JP ET AL: "Sequence effect of irinotecan (CPT-11) and topoisomerase II inhibitors in vivo." CANCER CHEMOTHER PHARMACOL, 1998, 42 (4) P327-35, XP002112007 GERMANY * abstract; p.334 * --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Y	US 5 532 218 A (BARGIOTTI ALBERTO ET AL) 2 July 1996 (1996-07-02) cited in the application claims 1,6,10	1-7

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